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# B cells in the pathophysiology of autoimmune neurological disorders: A credible therapeutic target

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## Abstract

There is evidence that B cells are involved in the pathophysiology of many neurological diseases, either in a causative or contributory role, via production of autoantibodies, cytokine secretion, or by acting as antigen-presenting cells leading to T cell activation. Clonal expansion of B cells either in situ or intrathecally and circulating autoantibodies are critical elements in multiple sclerosis (MS), Devic's disease, paraneoplastic central nervous system disorders, stiff-person syndrome, myasthenia gravis, autoimmune demyelinating neuropathies and dermatomyositis. The pathogenic role of B cells and autoantibodies in central and peripheral nervous system disorders, as reviewed here, provides a rationale for investigating whether depletion of B cells with new agents can improve clinical symptomatology and, potentially, restore immune function. Preliminary results from several clinical studies and case reports suggest that B cell depletion may become a viable alternative approach to the treatment of autoimmune neurological disorders.

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**Keywords:** B cells; Autoantibodies; Autoimmune neurological disorders; B cell depletion; Rituximab

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## 1. Introduction

During the last 20 years, there has been much emphasis on the role of activated T cells, T cell subsets or immunoregulatory T cells in the pathogenesis of autoimmune neurological disorders, most notably multiple sclerosis (MS) and Guillain-Barré syndrome (GBS). This focus on T cells probably relates to the observation that the main histopathological lesions in MS and GBS are dominated by mononuclear cell infiltrates (Hahn, 1998; Cross et al., 2001). It is also influenced by studies performed in their respective animal models, experimental autoimmune encephalomyelitis (EAE) and experimental autoimmune neuritis (EAN), where myelin-reactive T cells transfer the disease. However, emerging data from animal and human studies have renewed interest in the importance of B cells in the pathophysiology of autoimmune neurological disorders.

This review discusses the role of B cells, not only as antibody-producing cells, but also as cells participating in other components of the immune repertoire relevant to the pathogenesis of central nervous system (CNS) or peripheral nervous system (PNS) disorders. In addition, the pathogenic role of various autoantibodies associated with autoimmune neurological disorders are described alongside an examination of the possibility that infectious agents may promote cross-reacting autoantibodies with CNS or PNS antigens (molecular mimicry). Currently available treatments and the emerging role of agents that modulate B cells will be discussed in the context of the treatment of these diseases.

## 2. Biology of B cells

The adaptive immune system including the key elements—lymphocytes and antibodies—plays an important role in eliminating foreign microorganisms and molecules that may otherwise compromise health and wellbeing. B lymphocytes arise from hematopoietic stem cells and, after a clonal selection process, mature to produce antibodies specific for an antigen. In the bone marrow, stem cells mature independent of an antigen into pro-B cells, pre-B cells and immature B cells, which enter the antigen-dependent phase in the peripheral lymphoid tissues (Fig. 1). When these positively selected B cells are re-stimulated

with the relevant antigen, clonal expansion takes place giving rise, sequentially, to mature (naïve) B cells expressing surface IgM and IgD, activated B cells in the germinal center, memory B cells, early and late plasmablasts and finally antibody-producing plasma cells that are all specific for the original antigen (Fig. 1) (Goldsby et al., 2000; Sell, 2001; Avery et al., 2005). Specific cluster of differentiation (CD) markers such as CD19 and CD20 distinguish the B cells from stem cells and plasma cells, while others such as CD27, B cell activating factor for the TNF family (BAFF) and CD38, confer specificity for different B cell activation phases (Fig. 1).

Evidence indicates that B cells are involved in the pathophysiology of a number of diseases associated with pathogenic autoantibodies such as rheumatoid arthritis, systemic lupus erythematosus (SLE) and myasthenia gravis (Drachman, 1994; Edwards et al., 1999; Lipsky, 2001). All humans generate B cells that are autoreactive (i.e., have antiself reactivity). In the normal state, negative selection occurs at key points in the B cell development leading to tolerance, a process essential to ensure appropriate immune responses. Inappropriate responses, expressed as symptoms of autoimmune conditions, such as SLE, arise from a loss of self-tolerance resulting in the production of autoantibodies to a range of self-tissue antigens. Loss of tolerance may occur in the periphery, rather than centrally in the bone marrow and thymus, where the interaction of T cells with B cells amplifies the autoimmune process and leads to disease (Shlomchik et al., 2001). BAFF has now emerged as a powerful survival factor on B cells by stimulating the expression of pro-survival oncogene such as Bcl-2 (Mackay & Tangye, 2004). If BAFF is inappropriately expressed, it can promote the survival and escape of autoreactive B cells. Elevated BAFF levels have been detected in the tissues of several autoimmune diseases including the brains of MS patients (Krumbholz et al., 2005), and could explain the persistence of autoantibody production or T cell mediated tissue damage in these disorders.

## 3. Role of B cells: beyond antibody production

It has now become clear that B cells contribute to systemic autoimmunity and development of disease in several ways,

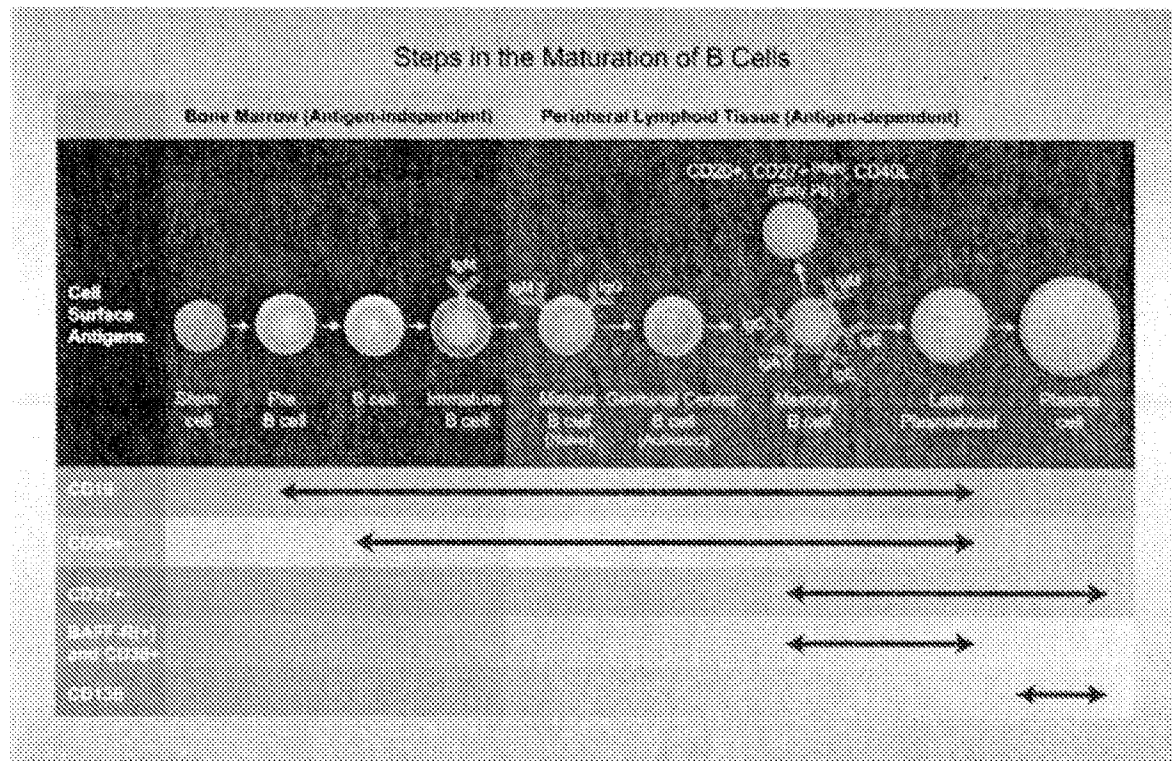


Fig. 1. B cells originate from hematopoietic stem cells within the adult bone marrow. Their maturation proceeds in two phases, antigen-independent in the bone marrow and antigen-dependent in the peripheral lymphoid tissue. The stem cells ( $CD19^+$  and  $CD20^-$ ) differentiate into pre-B cells ( $CD19^+$ ,  $CD20^-$ ) that express various cell adhesion molecules. Pre-B cells develop into immature B cells, that express IgM while still in the bone marrow, and evolve into mature (naive) B cells ( $CD20^+$ ,  $CD27^-$ ) that express IgM and IgD. The terminal B cell differentiation phase takes place in the germinal center from mature (naive) B cells upon activation by an antigen and costimulatory factors. In the germinal center, after Ig isotype switching, the naive B cells become activated and exit to differentiate into memory B cells ( $CD27^{low}$ ), early plasmablasts ( $CD27^{high}$ ,  $CD40L^+$ ) and "late" plasmablasts ( $CD27^+$ ,  $CD38^+$ ) that expresses BAFF (B cell-activating factor of the TNF family, also named BlyS). These cells migrate to the bone marrow, gut, spleen, tonsils but also brain under the direction of specific chemokines (CXCL12, CCL25, CCL28) where they evolve into antibody-producing plasma cells.

most notably via cytokine production, antigen presentation and complement activation (via autoantibody production) (Fig. 2). B cells secrete proinflammatory cytokines—interleukin 6 (IL-6), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and IL-10—which directly activate macrophages or alter the function of the other immunoregulatory cells. The production of IL-6 and IL-10 by B cells provides feedback stimulatory signals for further B cell proliferation and perpetuation of the cascade that leads to disease (Chan et al., 1999; Goldsby et al., 2000; Fillatreau et al., 2002; Duddy et al., 2004; Weinstein et al., 2004). Antigen-specific B cells are able to act as antigen-presenting cells and can interact with T cells. This leads to activation of the T cells (Constant, 1999), which in turn enhance antibody production by B cells through direct interaction with B cells and via cytokine production. This B cell–T cell interaction can result in simultaneous expansion of antigen-specific B cells and T cells, thus perpetuating and enhancing the immune response. It is postulated that this may occur in MS, as autoantibodies and T cells from MS patients have been shown to have very similar myelin basic protein (MBP) epitope specificity (Wucherpfennig et al., 1997). Autoantibodies produced by plasma cells derived from antigen-specific mature B cells recognise antigens on the cell surface of specific cells and initiate an acute inflammatory cascade, often by activating complement, which also results in

tissue damage. The Fc region of the antibody may also bind to Fc receptors on macrophages, neutrophils and NK cells causing those cells to specifically attack a targeted tissue by antibody-dependent cell-mediated cytotoxicity.

The evidence that B cells contribute to the pathophysiology of various autoimmune diseases through the above-mentioned functions is supported by a number of observations. For example, in rheumatoid arthritis, anti-immunoglobulin (IgG) antibodies, known as rheumatoid factors, are found in high titers in the synovium, and it has been proposed that rheumatoid factor-producing B cells may be pathogenic by functioning as antigen-presenting cells (Carson et al., 1991; Roosnek & Lanzavecchia, 1991). Furthermore, rituximab (MabThera<sup>®</sup>; Rituxan<sup>®</sup>), a chimeric anti-CD20 monoclonal antibody that eliminates  $CD20^+$  B cells, is beneficial in rheumatoid arthritis by depleting B cells without affecting the autoantibody levels (Edwards et al., 2004).

#### 4. Trafficking of B cells to the nervous system

Although it is believed that the CNS is immune privileged, it is now understood that, in the normal state, circulating immune cells cross the blood–brain barrier (Anthony et al., 2003). Indeed, human B cells migrate across the brain endothelium

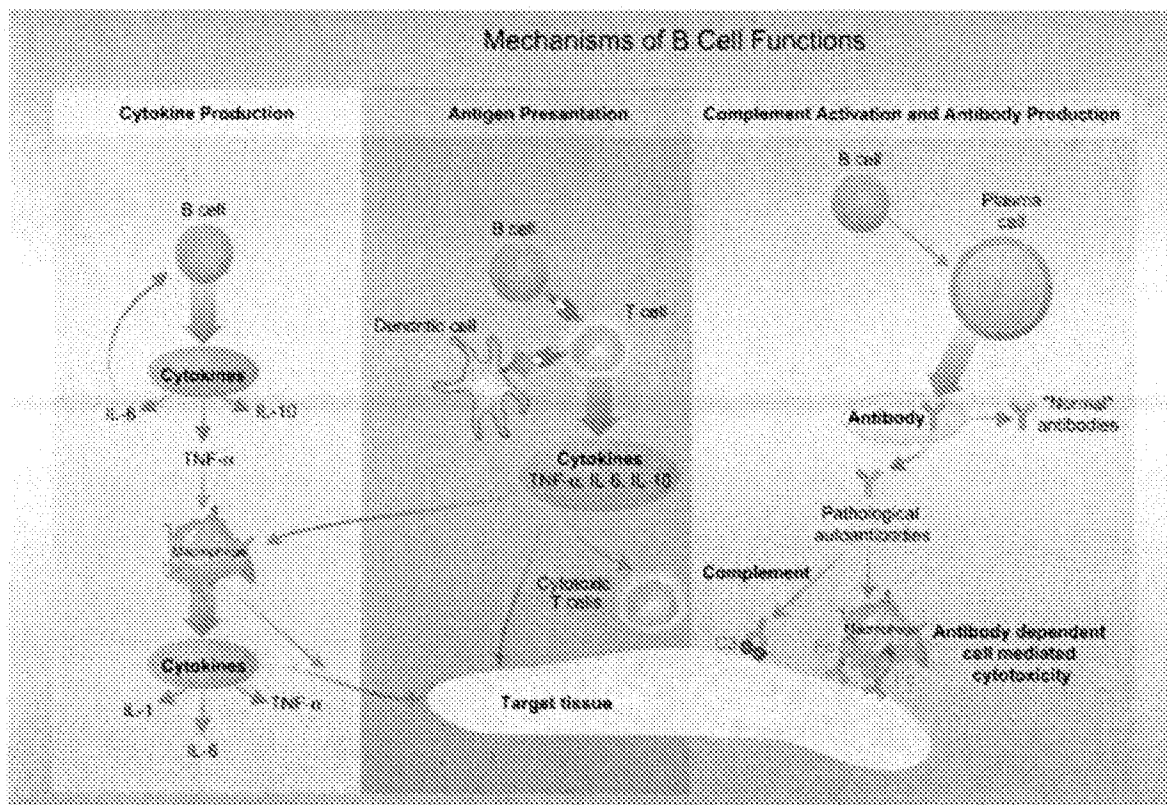


Fig. 2. The three main mechanisms by which B cells contribute to the pathology of immune-mediated conditions after their activation, include: **(a)** production of cytokines IL-6, TNF- $\alpha$ , IL-10 which activate macrophages and T cells and enhance tissue damage; **(b)** action as antigen-presenting cells (APC) resulting in clonal expansion of cytotoxic T cells and cytokine production; and **(c)** transformation(?) into plasma cells that produce antibodies. The antibodies cause tissue damage via complement activation or antibody-dependent-cell mediated cytotoxicity. (IL-6, interleukin 6; TNF- $\alpha$ , tumor necrosis factor alpha; IL-10, interleukin-10; IL-1, interleukin-1).

more rapidly than autologous T cells (Anthony et al., 2003). B cells are also capable of responding to an antigen within the CNS and differentiating into antibody-producing plasma cells, despite the presence of an intact blood–brain barrier (Knopf et al., 1998). Antigen-specific B cells appear to be able to enter all parts of the normal human brain, albeit in very low numbers (Anthony et al., 2003). Human B cells constitutively express the adhesion molecules VLA-4 and LFA-1, while their counter-receptors, VCAM-1 and ICAM-1, are upregulated on the blood–brain barrier endothelial cells by chemokines such as MCP-1 and IL-8 (Alter et al., 2003). During an inflammatory or immune demyelinating process the interaction of MCP-1 and IL-8 with their respective receptors on B cells, CCR2, CCR2a, CCR2b and CXCR1 and CXCR2, facilitates their transmigration within the CNS (Fig. 3) (Alter et al., 2003). In the CNS compartment, including the CSF, there is accumulation of memory B cells, early and late or short-lived plasmablasts, and plasma cell-secreting immunoglobulins (Ritchie et al., 2004; Cepok et al., 2005).

Emerging data from EAE and MS lesions indicate that B cells are important for initiating disease within the CNS (Raine et al., 1999; Genain et al., 1999). Data in B cell-deficient mice, for example, confirm that B cells contribute to the severity of myelin oligodendrocyte glycoprotein (MOG)-induced EAE (Svensson et al., 2002). In autoimmune neuropathies, although B cells and

plasma cells are rarely present within the endoneurial parenchyma, IgG or IgM antibodies secreted by the circulating B cells and plasma cells enter the nerve to recognise specific myelin or nerve antigens. In the muscle, B cells transmigrate to the endomysial spaces and are present in increased numbers around blood vessels in patients with dermatomyositis (Dalakas & Hohlfeld, 2003).

## 5. B cells, antibodies and molecular mimicry with nerve antigens

Molecular mimicry, a fundamental trigger of autoimmunity, is best defined as a dual recognition of molecules, common to an infectious agent (or tumor) and a host tissue, by a single B or T cell receptor. It is the mechanism by which infections or tumors trigger cross-reactive antibodies or T cells and may cause an autoimmune disease. Among the classic examples of molecular mimicry involving CNS or PNS tissues are HTLV-1-associated myelopathy and GBS with *Campylobacter jejuni* infection (Levin et al., 2002; Ang et al., 2004).

IgG antibodies against neurons isolated from patients with HTLV-1-associated myelopathy recognise a common epitope shared by neurons and HTLV-1 tax viral proteins. Because such reactive antibodies inhibit neuronal firing, this mimicry may be of clinical relevance (Levin et al., 2002). The greatest contribution of molecular mimicry to symptom expression at

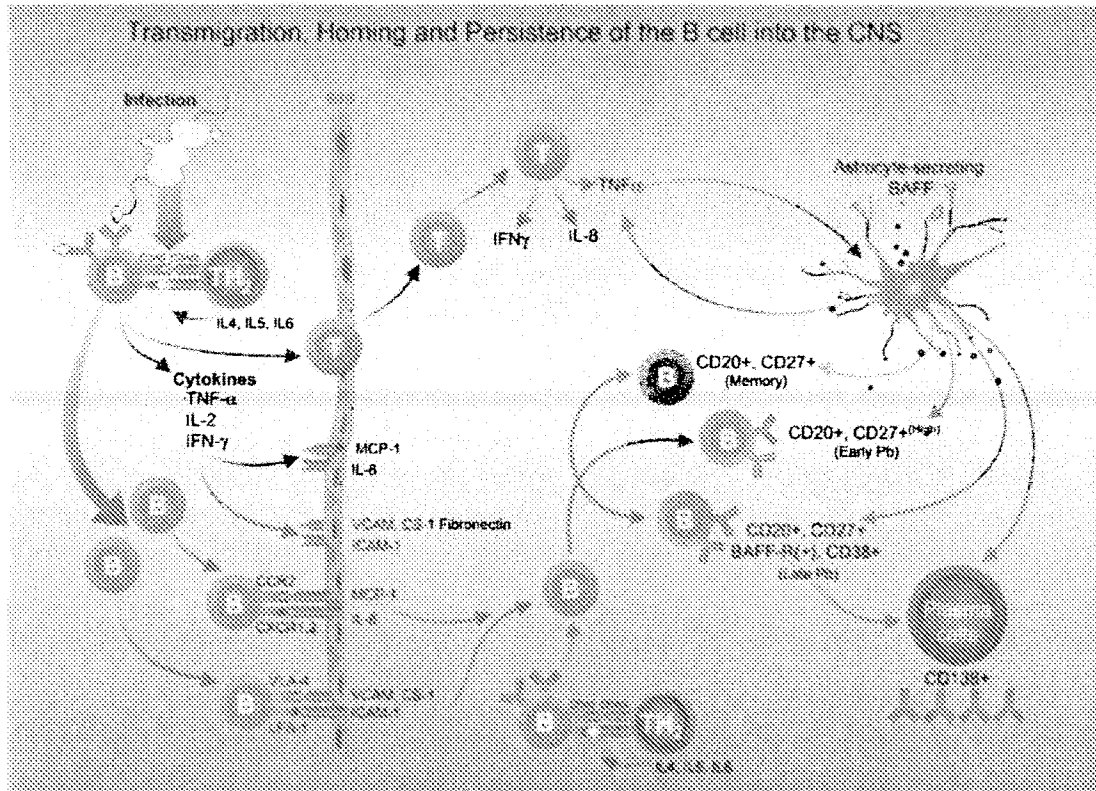


Fig. 3. Transmigration, homing and persistence of B cells into the nervous system. Circulating B cells constitutively express adhesion molecules VLA-4 and LFA-1 while the BBB (blood–brain barrier) endothelial cells constitutively express and secrete MCP-1 and IL-8 chemokines. After activation by an antigen (i.e., infection), B cells proliferate and release cytokines and chemokines, which upregulate VLA-4 and LFA-1 and the receptor for chemokines MCP-1 and IL-8 (CCR2, CCR2a, CCR2b and CXCR1, CXCR2). Activated B cells transmute via the adhesion molecule/chemokine receptors interactions (VLA-4/VCAM, LFA-1/ICAM-1, MCP-1/CCR2, IL-8/CXCR1) and home within the CNS. They may re-encounter the antigen at the site of antigen exposure leading to further B cell expansion and activation of cytokines and complement. There is evidence that in the CNS compartment, including CSF, there is accumulation of memory B cells, early and late plasmablasts, and immunoglobulin secreting plasma cells. BAFF is highly expressed on astrocytes of MS patients (Brod et al., 1996) and support the survival of BAFF-receptor expressing B cells allowing thereby the persistence and clonal expansion of B cells and continuous Ig production (i.e., persisting oligoclonal bands). Locally produced BAFF may also contribute to plasma cell survival in the CNS and to further T cell activation.

the B cell level has been demonstrated for GBS, which is triggered by the intestinal infection *C. jejuni* in approximately 25% of cases (Ogawara et al., 2000). This bacterial infection generates antibodies against the gangliosides GM1, GD1b or GD1a which are present on the myelin sheath; in turn, the IgG from GBS patients cross-reacts with oligosaccharide structures on *Campylobacter* which are identical to those present in the peripheral nerves (Willison & Yuki, 2002; Ang et al., 2004). Molecular mimicry has been also implicated in MS (Wekerle & Hoftfeld, 2003), stiff-person syndrome (Hassin-Baer et al., 2004) and paraneoplastic disorders (Roberts & Darnell, 2004).

## 6. The role of B cells in autoimmune neurological disorders

B cells and autoantibodies are involved in the pathogenesis of neurological diseases affecting all levels of the neuraxis, including brain and spinal cord (e.g., MS, neuromyelitis optica [Devic's disease], stiff-person syndrome and paraneoplastic CNS disorders), dorsal root ganglia and peripheral nerves (e.g., GBS and chronic demyelinating neuropathies), neuromuscular junction (e.g., myasthenia gravis) and muscle (e.g., dermatomyositis). The main observations supporting the role

of B cells in these disorders, as will be discussed, are summarised in Table 1.

### 6.1. Multiple sclerosis

MS is a complex autoimmune disease of the CNS characterised by demyelination and inflammation in the brain and spinal cord. The aetiology of MS is unknown, but it appears to be multifactorial. Evidence indicates that a pathogen—most likely a viral infection—triggers, possibly via molecular mimicry, an autoimmune attack against the myelin sheath of nerve cells in genetically susceptible individuals. Different patterns of demyelination, implying different pathogenic and pathophysiological mechanisms—especially with regard to the role of B cells and antibodies—appear to be involved in different stages of the disease or subgroups of MS (Lucchinetti et al., 2000). In the I–IV classification of Lucchinetti et al. for example, pattern II is characterized not only by prominent lymphocyte and macrophage infiltrates but also by complement activation and deposits of immunoglobulins (Lucchinetti et al., 2000) suggesting an antibody-mediated process (Lucchinetti et al., 2000). The improvement of these patients after therapeutic plasmapheresis

Table 1

Observations supporting the role of B cells in the pathophysiology of autoimmune neurological disorders

- B cells are clonally expanded within the central nervous system (CNS), producing intrathecal immunoglobulin (IgG), in various CNS disorders such as MS, paraneoplastic CNS disorders or stiff-person syndrome.
- B cells, plasma cells and myelin-specific IgG are present in the active and chronic plaques of MS.
- B cells are required for disease induction by antigenic peptides in experimental autoimmune encephalomyelitis (EAE) and experimental autoimmune neuritis (EAN) models, consistent with the B cells' unique ability to recognise antigenic conformation.
- B cells play a role in oligodendrocyte glycoprotein-induced EAE model.
- B cells are essential in regulating CNS inflammation.
- Autoantibodies against glycolipids and glycoproteins can induce demyelination within the peripheral nervous system (PNS).
- T cell dependent B cell activation leads to production of pathogenic autoantibodies in myasthenia gravis.
- The successful treatment of several antibody-mediated neurological disorders using plasmapheresis or intravenous immunoglobulin (IVIg) that remove autoantibodies or modify the idiotypic repertoire.
- New therapeutic monoclonal antibodies like rituximab that act as 'guided missiles' to deplete B cells result in clinical improvement when used in certain CNS or PNS disorders.

supports the humoral mediated process (Keegan et al., 2005). Additional evidence is supported by the presence of clonally expanded accumulations of B cells in the plaques of chronic MS lesions along with intrathecal B cell clonal selection and expansion and the presence of oligoclonal IgG bands derived from the oligoclonal population of B cells in the brain and cerebrospinal fluid (CSF) (Qin et al., 1998; Baranzini et al., 1999; Colombo et al., 2000; Williamson et al., 2001; Owens et al., 2003; Qin et al., 2003). A high percentage of CD5<sup>+</sup> B cells, a B cell subset responsible for the secretion of IgM antibodies against nonprotein antigens, is also found in MS patients (Mix et al., 1990).

Furthermore, ectopic lymphoid follicles have been recently demonstrated in the meninges of patients with secondary progressive MS (Serafini et al., 2004) that may be involved in maintaining the intrathecal B cell antibody response. Compartmentalised B cell response was also found to occur within the CNS of MS patients through a recapitulation of all stages of B cell differentiation, similar to that observed in secondary lymphoid organs (Corcione et al., 2004). In addition, tissue-bound IgG and complement are localised to the areas of demyelination (Compston et al., 1989; Lucchinetti et al., 2000). High B cell and low monocyte numbers are also seen in the CSF of MS patients and correlate with the rate of disease progression in the relapsing–remitting and secondary progressive forms of the disease (Cepok et al., 2001). Intrathecal production of IgM anti-myelin antibodies also appears to be a predictor of aggressive evolution in MS patients (Villar et al., 2005). Moreover, memory B cells and upregulation of co-stimulatory molecules such as CD80 have been noted in MS lesions, which may serve as antigen-presenting cells to sustain T cell activation (Genç et al., 1997; Bar-Or et al., 2001).

Evidence suggests that autoantibodies specific for myelin proteins—in particular, MOG—may play a role in the initiation or progression of the inflammatory process in MS. MOG is a

minor CNS-specific component of the myelin which is preferentially expressed on the outermost surface of the sheath (Genain et al., 1999). Demyelinating lesions seen in MOG-induced EAE in the rat and marmoset models are very similar to those seen in MS (Storch et al., 1998; Mancardi et al., 2000). Data in B cell-deficient mice suggest that B cells contribute to the severity of the MOG-induced EAE model (Svensson et al., 2002). In tissue from humans with MS and primates with EAE, autoantibodies against MOG, along with complement, have been localised in the actively demyelinating lesions (Genain et al., 1999; Raine et al., 1999; Lucchinetti et al., 2000). Furthermore, antibodies against MOG are detectable early in a large subgroup of patients with MS. These antibodies seem to persist over time and, if confirmed with additional studies, appear to have prognostic value (Reindl et al., 1999; Berger et al., 2003). Although all of the aforementioned observations are highly suggestive of an antigen-driven immune response, the contribution of B cells to MS pathogenesis is complex, because cytotoxic and immunoregulatory T cells are also involved.

## 6.2. Neuromyelitis optica

In neuromyelitis optica, patients exhibit symptoms of optic neuritis and myelopathy without other neurological signs (Lucchinetti et al., 2002; Wingerchuk, 2004). Examination of lesions from autopsy cases has revealed Ig deposits, predominantly IgM, and complement on the endothelial cell wall, resulting in vascular damage (Wingerchuk, 2004). The role of humoral mechanisms in the pathogenesis of the disease is further supported by the recent finding that a number of these patients have an autoantibody against aquaporin-4 water channel on the CNS endothelial cells (Lennon et al., 2005).

## 6.3. Paraneoplastic neurological syndromes

Paraneoplastic neurological syndromes are non-metastatic neurological complications occurring in patients with cancer (Vltz, 2002; Darnell & Posner, 2003). It is believed that when antigens normally restricted to the nervous system are expressed in a non-nervous system cancer, such as small-cell lung cancer (SCLC), ovarian cancer or breast cancer, the immune system recognises the neural antigen in the cancer as foreign and mounts an immune attack, resulting in the production of serum antibodies. Serum antibodies are detected in all patients with paraneoplastic syndromes, among which the most common are anti-Hu antibodies seen in patients with encephalomyelitis, sensory neuronopathy or cerebellar ataxia (Dalmau et al., 1992; Graus et al., 2001; Vltz, 2002; Darnell & Posner, 2003), and anti-Yo antibodies seen in cerebellar degeneration (Peterson et al., 1992). Other such antibodies include anti-Ri antibodies seen in patients with brainstem encephalitis (Jensen et al., 2000), anti-Ma1 and anti-Ma2 antibodies seen in limbic encephalitis in association with testicular or lung cancer (Rosenfeld et al., 2001), anti-amphiphysin or antigeophysin antibodies seen in stiff-person syndrome in association with breast cancer (Yu et al., 2001), anti-voltage-gated calcium channel (VGCC) antibodies seen in Lambert-Eaton myasthenic syndrome (LEMS) in conjunction

with SCLC (Carpentier & Delattre, 2001), and anti-voltage gated potassium channel (VGKC) antibody seen in neuromyotonia associated with thymoma or SCLC (Hart et al., 2002).

In paraneoplastic CNS disorders, B cells, plasma cells and cytotoxic T cells cross the blood–brain barrier and there is evidence that antibodies are synthesised in situ by the B cells that reside within the CNS. B cells with the CD19 phenotype and clonal expansion of B cells with CD5<sup>+</sup> phenotype have been found in high numbers in the CSF of opsoclonus-myoclonus patients, and their number correlates with clinical severity (Pranzatelli et al., 2004a, 2004b). Although antibodies appear to have a predominant role (Darnell & Posner, 2003), the exact humoral and cellular pathways involved in the pathophysiology of these syndromes have not been clarified, and the means by which the immune system recognises such intracellular antigens remains unclear.

#### 6.4. Stiff-person syndrome and anti-glutamic acid decarboxylase-cerebellar ataxias

Stiff-person syndrome is a rare disorder that commonly involves rigidity of trunk and leg muscles with episodic muscle spasms (Dalakas et al., 2000). A high proportion of patients have antibodies against glutamic acid decarboxylase (GAD)—the enzyme necessary for synthesis of gamma-aminobutyric acid (GABA), the brain's predominant inhibitory neurotransmitter (Solimena et al., 1990). These antibodies are synthesised intrathecally, presumably by B cells that have crossed the blood–brain barrier (Dalakas et al., 2001). In addition, oligoclonal IgG bands similar to those seen in MS patients are very commonly detected in the CSF (Dalakas et al., 2001). The pathogenic role of anti-GAD antibodies in stiff-person syndrome remains unclear but in vitro data suggest that they inhibit GAD activity, resulting in reduced GABA levels in the brain or CSF (Dinkel et al., 1998; Raju et al., 2005). A small subset of patients with acquired cerebellar ataxia also have anti-GAD antibodies which may serve as markers of an ongoing autoimmune process involving cerebellar neurons.

#### 6.5. Myasthenia gravis

Myasthenia gravis is a prototypic B cell-mediated autoimmune disease caused by pathogenic antibodies directed against the muscle acetylcholine receptor (AChR) (Drachman, 1994; Ragheb & Lisak, 1998; Vincent et al., 2000). Although B cells are not seen in the end-plate region, the pathogenic antibodies produced by the peripherally stimulated plasma cells freely enter there. These antibodies reduce the amount of functional receptors on the postsynaptic membrane by a number of mechanisms, including internalization or degradation of the receptor, triggering complement-mediated focal destruction of the postsynaptic membrane (Drachman, 1994; Vincent et al., 2000).

The pathogenic role of AChR antibodies has been clearly established. As proof of principle, myasthenic IgG transmits the disease, whereas removal of the AChR antibodies (via plasmapheresis) results in clinical improvement (Drachman, 1994; Vincent et al., 2000). The pathogenic significance of anti-

MuSk antibodies, found in a subset of patients with AChR-negative MG, remains still unclear; these patients, however, respond to immunotherapy and the disease can be transmitted to animals suggesting a humoral-mediated process (Vincent & Leite, 2005).

#### 6.6. Lambert-Eaton myasthenic syndrome

LEMS is characterised by antibodies directed against VGCC at the presynaptic nerve terminals (Vincent et al., 2000; Darnell & Posner, 2003). Similar to the situation in myasthenia gravis, the pathogenic role of these antibodies has also been established; the patient's serum transmits the disease and removal of the antibodies with plasmapheresis results in clinical improvement (Vincent et al., 2000).

#### 6.7. Anti-voltage gated potassium channel-associated neuromyotonia and limbic encephalitis

Neuromyotonia, a disorder of peripheral nerve excitability, and non-paraneoplastic limbic encephalitis that presents with subacute confusional state, are characterized by antibodies to VGKC. In neuromyotonia, the pathogenic role of these antibodies has been demonstrated by passive transfer of relevant electrophysiologic changes to mice by injection of patients' IgG (Buckley & Vincent, 2005). Further, neuromyotonia and limbic encephalitis respond to plasmapheresis, intravenous immunoglobulin (IVIg) or immunosuppressive agents (Vincent et al., 2004).

#### 6.8. Dermatomyositis

Dermatomyositis is an inflammatory disease that affects muscle and skin (Dalakas & Hohlfeld, 2003). The disease occurs when activation of complement, presumably by antibodies directed against endothelial cells, causes lysis of the endomysial capillaries and muscle ischemia (Dalakas & Hohlfeld, 2003). B cells are the predominant lymphocytes among the endomysial infiltrates (Engel & Arahata, 1986). A direct correlation also exists between increased numbers of peripheral blood B cells and worsening of the disease (Eisenstein et al., 1997). Although dermatomyositis may be a humorally mediated process, the putative antigen and the responsible antibody have not yet been identified (Dalakas & Hohlfeld, 2003).

#### 6.9. Guillain-Barré syndrome

GBS is an acute demyelinating disease of the PNS which is thought to be triggered by a preceding bacterial or viral infection. The disease is characterised by 4 main subtypes: acute inflammatory demyelinating polyneuropathy (AIDP); acute motor axonal neuropathy (AMAN); acute motor sensory axonal neuropathy (AMSAN); and Miller Fisher syndrome (MFS). Although they have some similarities in their clinical and electrophysiological features, the implicated antigen/s may be different because the immune attack appears to be directed at different targets: Schwann cell surface membrane or the myelin in AIDP, the axonal membrane in motor fibres in AMAN, both

motor and sensory nerve fibres in AMSAN, and nodal regions of the ocular motor nerve and distal nerve terminals in MFS (Willison & Yuki, 2002; Kuwabara, 2004).

Antibodies against gangliosides have been consistently detected in 2 subtypes of GBS: AMAN and MFS. Antibodies to gangliosides GM1, GM1b, GD1 or GalNAc-GD1a are thought to play a role in the pathogenesis of AMAN (Ogawara et al., 2000; Willison & Yuki, 2002), and antibodies against GQ1b in the pathogenesis of MFS (Chiba et al., 1993; Willison & Yuki, 2002). IgG and complement are also deposited in the nerves (Hafer-Macko et al., 1996). Molecular mimicry triggered by *C. jejuni* is the implicated mechanism in AMAN (as discussed earlier). This bacterial infection generates antibodies against the gangliosides GM1, GD1b or GD1a which are present on the myelin sheath; in turn, the IgG from GBS patients cross-reacts with oligosaccharide structures on *C. jejuni* which are identical to those present in the peripheral nerves (Ogawara et al., 2000; Willison & Yuki, 2002; Ang et al., 2004; Yuki et al., 2004). Although the pathogenesis of GBS is not fully understood and both T and B cells are involved, in at least some subtypes the disease is most likely mediated by complement-fixing antibodies, which are responsible for demyelination and conduction block (Kieseier et al., 2004).

#### 6.10. Chronic, antibody-associated demyelinating polyneuropathies

There are 3 main subsets of antibody-associated polyneuropathy: chronic inflammatory demyelinating polyneuropathy (CIDP), multifocal motor neuropathy (MMN) and IgM anti-myelin-associated glycoprotein (MAG) demyelinating neuropathy (Kornberg & Pestronk, 2003; Czaplinski & Steck, 2004; Kieseier et al., 2004). In CIDP, both cellular and humoral mediated mechanisms are involved. The implicated antibodies, although not proven to be pathogenic, are directed against glycolipids, GM1 or Po (Yan et al., 2000). IgG and complement are deposited in the nerves (Dalakas & Engel, 1980; Hays et al., 1988). In half of the patients with multifocal motor neuropathies, IgG GM1 antibodies are detected (Nobile-Orazio, 2001) but their pathogenic role has not been established. In anti-MAG neuropathies, the antibodies are directed against MAG or glycolipids and are produced by a monoclonal population of plasma cells (Ropper & Gorson, 1998; Dalakas, 2001; Nobile-Orazio, 2004). These antibodies are thought to be pathogenic because IgM is deposited on the myelin and splits the myelin lamellae, anti-MAG antibodies can transfer the disease to animals, and IgM anti-MAG disrupts normal cellular interactions by activating the complement pathway (Latov, 1994; Dalakas & Quarles, 1996; Ropper & Gorson, 1998; Quarles & Weiss, 1999; Dalakas, 2001; Nobile-Orazio, 2004).

### 7. Agents currently used for the treatment of autoimmune neurological disorders

Given the role of the immune system in the pathogenesis of these disorders, immunomodulatory treatment is often used.

However, the applied immunotherapies are not targeted directly to B cells or the disease-specific autoantibodies, and include various immunosuppressants or immunomodulating drugs and procedures used for both T and B cell-mediated disorders. The following agents are currently used (Gold et al., 2003; Hohlfeld & Dalakas, 2003).

#### 7.1. Glucocorticoids

Glucocorticoids are the most widely and frequently used drugs in the treatment of these disorders. Steroids, by modifying immunoregulatory transcription factors, have an effect on cytokines and T cell functions, causing a shift from Th<sub>1</sub> to Th<sub>2</sub> cytokine production (Daynes & Araneo, 1989), and the distribution and trafficking of T cells and macrophages. It is unclear, however, if steroids have an effect on antigen-presenting cells, B cells or their trafficking to the CNS. Their effect on antibody production seems to be insignificant, although steroids are effective in certain antibody-mediated neurological disorders such as myasthenia gravis and LEMS, and decrease IgG synthesis in the CSF of MS patients (Smith et al., 1998). Their effect in disorders that are caused by combined humoral and T cell-mediated mechanisms is mixed. For example, they are effective in acute relapses of MS patients, in myasthenia gravis, CIDP and dermatomyositis but not in GBS, anti-MAG-mediated neuropathies, paraneoplastic disorders, or primary progressive MS (Smith et al., 1998; Gold et al., 2003; Hohlfeld & Dalakas, 2003).

#### 7.2. Azathioprine and mycophenolate mofetil

Azathioprine (AZA) and mycophenolate mofetil (MMF) act primarily on proliferating lymphocytes (Lipsky, 1996). In vitro studies with AZA have demonstrated effects on both T and B cell functions, including antibody responses. These drugs appear helpful as steroid-sparing agents in certain autoimmune or antibody-mediated disorders such as MS, myasthenia gravis, LEMS, CIDP and dermatomyositis (Smith et al., 1998; Chaudhry et al., 2001; Cifaloni et al., 2001), but they are ineffective in stiff-person syndrome, paraneoplastic disorders, MMN or anti-MAG neuropathy patients.

#### 7.3. Immunophilin-binding agents (cyclosporine, sirolimus, tacrolimus)

Cyclosporine and tacrolimus inhibit the phosphate calcineurin and its substrate, the nuclear factor of activating T cells (NFAT), and prevent the transcription of mRNA for key cytokines including IL-2 (Abraham, 1998; Guo et al., 2001; Hohlfeld & Dalakas, 2003; Gold et al., 2003). Sirolimus acts by controlling phosphorylation of proteins involved in the cell cycle. Cyclosporine offers a marginal benefit in MS (Rudge et al., 1989) and is ineffective in anti-MAG neuropathy, but provides some help in myasthenia gravis (Tindall et al., 1987) and CIDP. Tacrolimus, in preliminary studies, seems to be promising in patients with MG (Vincent & Leite, 2005).



#### 7.4. Methotrexate

Methotrexate inhibits the enzyme dihydrofolate reductase and affects purine and thymidine biosynthesis. As a result, it acts on rapidly dividing cells. Methotrexate has shown some benefit, mostly in the upper extremities, of MS patients (Goodkin et al., 1995) but it is generally of limited benefit in the autoimmune neurological disorders discussed above. It is predominantly used in dermatomyositis.

#### 7.5. Cyclophosphamide

Cyclophosphamide is an alkylating agent able to intercalate into the DNA helix, and which acts on rapidly dividing cells. Cyclophosphamide affects the numbers and functions of T and B cells. It is of help to some patients with MS (Smith et al., 1998), myasthenia gravis, dermatomyositis and CIDP, but long-term serious toxicity limits its use. In myasthenia gravis, very high doses of cyclophosphamide are said to “reboot” the immune system, with very promising preliminary results in a limited number of patients (Drachman et al., 2003).

#### 7.6. Mitoxantrone

Mitoxantrone acts on both DNA and RNA synthesis. It causes apoptosis of B cells and preferentially the CD19-positive cells (Chan et al., 2005), but also other antigen-presenting cells. It also inhibits the activation of T helper cells and cytokines (Neuhaus et al., 2004). It has been shown to exhibit clinical effectiveness in MS, but has not been systematically studied in other B cell-mediated neurological disorders (Jacobs et al., 1996). Cardiotoxicity limits its use beyond a 2-year period.

#### 7.7. Interferon- $\beta$

Interferon (IFN)- $\beta$  preparations (IFN- $\beta$ 1b and IFN- $\beta$ 1a) exert an immunomodulating action, probably by affecting the expression or modulation of MHC-II molecules, metalloproteinases, and cytokines or, theoretically, by exerting an antiviral effect against elusive viruses. They are effective in relapsing–remitting MS but not in secondary progressive MS, CIDP or GBS (Dayal et al., 1995; Brod et al., 1996; IFNB Multiple Sclerosis Study Group & UBC MS-MRI Analysis Group, 1996). IFN- $\beta$  is not used in other B cell or antibody-mediated neurological disorders.

#### 7.8. Glatiramer acetate

Glatiramer acetate (formerly known as copolymer-1) is a synthetic copolymer of L-glutamic acid, L-alanine, L-lysine and L-tyrosine. It probably induces regulatory T cells which affect T-cell mediated inflammation in MS lesions. Glatiramer acetate may also induce an antibody-mediated repair of demyelinated lesions (Ure & Rodriguez, 2002). It is effective in relapsing–remitting MS but not in primary or secondary progressive MS.

#### 7.9. Intravenous immunoglobulin

Prepared from IgG from healthy donors, IVIg has multiple actions on the immune repertoire, including an effect on circulating antibodies by supplying idiotypes or affecting antibody production, suppressing cytokines, inhibiting complement activation, modulating Fc receptors on macrophages and interfering with antigen recognition (Kazatchkine & Kaveri, 2001; Dalakas, 2004). IVIg has been shown to be effective in B cell or antibody-mediated neurological disorders including myasthenia gravis, LEMS, stiff-person syndrome and dermatomyositis. IVIg is also effective in disorders where both B cells and T cells are critical, including CIDP, GBS, MMN and relapsing–remitting MS. IVIg is not effective in anti-MAG neuropathies, paraneoplastic syndromes or chronic progressive MS (Dalakas, 2004).

#### 7.10. Plasmapheresis

Plasmapheresis removes autoantibodies and inflammatory mediators. It offers substantial benefit in the treatment of autoantibody-mediated diseases such as myasthenia gravis and LEMS. Plasmapheresis is also effective in GBS and CIDP, and may offer some benefit in patients with Devic’s disease and in some cases with acute severe attacks of CNS inflammatory demyelination (Keegan et al., 2002). Plasmapheresis is not effective in MMN, anti-MAG demyelinating neuropathies, paraneoplastic syndromes and dermatomyositis.

#### 7.11. Bone marrow or peripheral blood hematopoietic stem cell transplantation

Intense immunosuppression (immunoablation) followed by allogeneic or autologous hematopoietic stem cell transplantation (HSCT) has been advocated in some autoimmune disorders (van Bakkum, 2000; Fassas et al., 2002). Preliminary experience in patients with MS suggests that the procedure is feasible with some positive results but with significant mortality (van Bakkum, 2000; Fassas et al., 2002).

### 8. The merit of B cell depletion using new agents in the treatment of neurological disorders: evidence beyond autoantibody reduction

The pathogenic role of autoantibodies in the CNS and PNS disorders discussed above provides a sound rationale for investigating whether the depletion of B cells will improve clinical signs and symptoms of neurological disorders and, potentially, restore normal immune function. This approach would offer the potential of an alternative therapy to the management of these diseases, particularly as many have no curative treatment. Depletion of B cells may be beneficial not only by reducing antibody production, but also by inhibiting the antigen-presenting role of B cells and the cytokine network which is fundamental for stimulating T cells and macrophages. Two approaches that affect B cells and show potential as targeted therapy in the treatment of autoimmune neurological

disorders are antagonism of B lymphocyte stimulator (BLyS) protein on B cells [also called BAFF (Fig. 1)], which is being evaluated as therapy for SLE, and the use of the monoclonal anti-B-cell antibody rituximab, which is being evaluated in a number of autoimmune neurological disorders. In patients with B cell or autoantibody-mediated disorders which are inadequately responsive to any of the traditional treatment modalities, such as chronic progressive MS, paraneoplastic disorders and anti-MAG neuropathy, these drugs may offer a promising new mode of therapy. They may also provide a more targeted and effective therapy in some of the other disorders previously described, including myasthenia gravis, stiff-person syndrome, dermatomyositis, MMN or CIDP, when patients have become unresponsive or are inadequately controlled with the established agents.

A human anti-BLyS monoclonal antibody, belimumab (LymphoStat-B™), inhibits BLyS-induced proliferation of B cells *in vitro*, prevents human BLyS-induced increases in splenic B cell numbers and IgA titers in mice, and causes B cell depletion in the spleen and lymph node of cynomolgus monkeys (Baker et al., 2003). In a Phase I study in SLE, belimumab appeared to be well tolerated and caused a reduction in circulating CD20<sup>+</sup> B cells (Stohl, 2004). Further clinical investigation of belimumab is ongoing and several other anti-BLyS antagonists, as well as agents that target BLyS receptors on B cells, are in development for use in humans. However, their utility in neurological disorders is unknown at present. Anti-BLyS (BAFF) therapy could be an attractive target for MS because BAFF is inappropriately upregulated in the MS brain (Krumbholz et al., 2005). Because elevated BAFF levels have been seen in other autoimmune disorders and prolong the survival of autoreactive B cells (Mackay & Tangye, 2004), targeting this subpopulation of B cells could be a viable therapeutic option.

Rituximab is a genetically engineered chimeric anti-CD20 monoclonal antibody approved for the treatment of relapsed or refractory low-grade or follicular CD20-positive B cell non-Hodgkin's lymphoma. Rituximab causes selective depletion of CD20-positive pre-B and mature B cells, but not stem cells or plasma cells (Fig. 1). Multiple mechanisms have been proposed to be involved in rituximab-induced B cell depletion, including antibody-dependent cellular cytotoxicity, complement mediated cell lysis, and induction of apoptosis of B cells (Reff et al., 1994). Rituximab may have a synergistic apoptotic effect with steroids. However, its effect on B cell depletion is transient and B cell repopulation begins to occur from the unaffected stem cells and after 6 months (McLaughlin et al., 1998; Grillo-Lopez et al., 2002).

The B cell depletion induced by rituximab may not only decrease *de novo* antibody production, but could also inhibit the role of B cells as antigen-presenting cells and can down-regulate the important co-stimulatory signals required for clonal expansion of T cells. Further, B cell depletion could have an effect on activation of macrophages or formation of immune complexes, because B cells activate macrophages and complement via TNF- $\alpha$ , IL-6 and IL-10 (as discussed previously). As a result, rituximab-induced B cell depletion may be beneficial in

theory not only to antibody-mediated disorders of the CNS or PNS such as stiff-person syndrome, myasthenia gravis and MMN, but also for those where both B and T cells contribute to disease pathogenesis, such as MS, CIDP, GBS and paraneoplastic disorders.

Preliminary results with rituximab in autoimmune neurological disorders are encouraging, and suggest that further investigation in controlled trials is warranted. Case reports or prospective open-label studies have shown that rituximab can improve neurological symptoms in the treatment of a range of diseases, such as Dermatomyositis (Levine, 2005), myasthenia gravis (Zaja et al., 2000; Wylam et al., 2003), demyelinating IgM neuropathies, CIDP or multifocal motor neuropathies (Levine & Pestronk, 1999; Kasamon et al., 2002; Pestronk et al., 2003; Renaud et al., 2003; Ruegg et al., 2004), certain paraneoplastic autoimmune neurological conditions (Weide et al., 2000; Arzoo et al., 2002; Liberato et al., 2003; Sansonno et al., 2003), and MS (Stuve et al., 2005). An effect in primary progressive MS may be due to depletion of B cells in the periphery rather than within the CSF (Monson et al., 2005). Most importantly, rituximab appears to be well tolerated in non-malignant disorders. In some controlled trials, such as a study conducted in rheumatoid arthritis, rituximab appears to have a synergistic effect with immunosuppressants (i.e., methotrexate) without potentiating or precipitating any additional side effects (Edwards et al., 2004). Future clinical trials are required to clarify this finding.

## 9. Conclusions

There is no doubt that B cells play an important role in the pathomechanisms of certain autoimmune neurological conditions, some of which respond poorly to available therapies. Results from human and animal studies have improved our understanding of B cell physiology in neurological disease, which may have important therapeutic implications. Modulation of B cell function, such as B cell depletion, provides a novel approach to the treatment of neurological disorders not only by affecting autoantibodies but also by inhibiting the role of B cells as antigen-presenting cells and downregulating the clonal expansion of T cells. As such, B cell depletion using specific monoclonal antibodies has the potential to be a valuable therapeutic approach for the treatment of MS, autoimmune neuropathies, dermatomyositis, myasthenia gravis or paraneoplastic CNS diseases. Controlled clinical trials using B cell targeted therapies are needed to confirm the potential benefit of this novel and promising therapeutic option.

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